Outcome on Diabetic Foot Complications in Relation to Clinical Examination and Quantitative Sensory Testing: a Case–control Study

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A total of 405 diabetic patients who first attended St Thomas' Diabetes Clinic between 1982 and 1985 had a detailed standardized computerized first visit record, including a structured foot examination and toe vibration perception thresholds (VPT, Biothesiometer), were reviewed in 1995. None of the patients had a history of foot ulceration at first visit. Twenty-five patients (6.2 %) developed foot ulcers ($n = 11$, 2.7 %) or had an amputation ($n = 14$, 3.5 %) over a mean 12-year period. Twenty of these patients were then individually matched with 3 non-ulcer patients. Statistically significant odds ratios (OR) were found for a baseline abnormal age-adjusted toe VPT (OR 4.38, CI 1.11–17.26; $p = 0.01$); abnormal clinical examination (at least 1 abnormality out of: ankle jerks, tuning fork or cotton wool sensation; OR 2.3, CI 1.00–5.20; $p < 0.01$); and HbA_1 (OR 1.30, CI 1.01–1.66; $P < 0.02$) in patients who subsequently developed lower extremity complications. The sensitivity of VPT (70 %) was better than that for clinical testing (55 %) in predicting long-term complications, although all tests showed similar specificity (70–72 %). The risk of events also doubled for every 10 years of diabetes (OR 2.10, CI 1.11–4.30; $p = 0.02$). We conclude that age-corrected VPT measurements, which are objective and simple to perform, are better predictors of future foot complications than semi-quantitative tests in diabetes clinics. We encourage their use in the campaign to reduce the morbidity of diabetic peripheral neuropathy. © 1998 John Wiley & Sons, Ltd.

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Introduction

People with diabetes have a 15-fold higher risk of amputation than people with no diabetes.[1] Diabetic foot ulcers precede amputations in about 85 % of cases.[2] Both neuropathic foot ulceration and amputation are associated with an increased morbidity and mortality.[3,4] In the USA, lower extremity amputations cost about $25 000 per case.[5] The major risk factors for lower extremity ulceration and amputation are peripheral neuropathy and peripheral vascular disease. Other diabetic complications, notably proteinuria,[6] limited joint mobility[7] and high dynamic foot pressures[8] have all been associated with plantar ulceration. The Diabetes Control and Complications Trial (DCCT)[9] has established that a lowering of HbA_{1c} in patients with Type 1 diabetes was associated with a reduction in subsequent development of clinical neuropathy but did not examine lower extremity ulceration or amputation as a major outcome variable. In order to define the risks for such diabetic foot disease, we report a 12-year analysis of risk factors in a cohort of 405 patients who first attended the Diabetes Clinic at St Thomas' between 1982 and 1985. The main objective of our study was to identify high risk patients in a typical diabetes clinic setting.

Patients and Methods

Since 1982, all patients first attending the diabetes clinic at St Thomas' Hospital have a structured and comprehensive standardized first visit record carried out directly on our computer database (Diabeta). As this is not attached to a specialist foot clinic, the patients are not at particularly high risk for lower extremity complications. Our population of patients is multi-ethnic and has the expected distribution of age (range 18–90 years), gender (male 53.9 %), and type of diabetes (Type 1 DM 37.4 %) of a UK hospital diabetes clinic.[10] Nine hundred and eighty-five new patients had a first visit between January 1982 and September 1985. Data entered in the computer include a structured clinical examination

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of the lower limbs and Vibration Perception Threshold (VPT) measurements, made using a hand-held biothesiometer (Biomedical Instruments, Newbury, Ohio, USA). VPTs were measured at the pulp of the thumbs and great toes and at the medial malleoli. The voltage reading from the biothesiometer at each site is entered into the computer during the consultation. The computer calculates a 'standard deviation score' (SDS) by comparing the patient's value with that from an age-related normal population. The 'standard deviation score' is the number of standard deviations that the individual's reading is away from the age-related mean.[11,12] In normal subjects there is a linear relationship between the logarithm of the biothesiometer voltage reading against age. The standard deviation score (SDS) is calculated by the equation:

$$\mathrm{SDS} = \frac{(\log_{10}\mathrm{bio}_0) - (\log_{10}\mathrm{bio}_m)}{s} \qquad \text{(a)}$$

where bio_0 is the observed reading on the biothesiometer (in volts), bio_m is the normalized value (mean of normal subjects) and s is the residual standard deviation of the normalized value. The normalized value is calculated from a linear fit to the logarithm of normal data of biothesiometer reading against age in years.

$$(\log_{10}\mathrm{bio}_m) = \frac{(\mathrm{slope} \times \mathrm{age}) + \mathrm{intercept}}{s} \qquad \text{(b)}$$

Substituting for $(\log_{10}\mathrm{bio}_m)$ in equation (b)

$$\mathrm{SDS} = \frac{(\log_{10}\mathrm{bio}_0) - (\mathrm{slope} \times \mathrm{age}) + \mathrm{intercept}}{s} \qquad \text{(c)}$$

The different sites normalized (thumb, great toe, medial malleolus) show different variation with age, and the slopes, intercepts and standard deviations (s) are derived from Bloom *et al.*[11]

A standard deviation score of +1.96 corresponds to the 95th centile, and thus scores above 1.96 are taken to be abnormally high. So given a subject's reading (bio_m) and their age and the parameters in equation (b), the reading can be normalized for age, using equation (c). In this study, an abnormal toe VPT was defined as a standard deviation score > 1.96 at one or both great toes.

Bedside clinical tests performed at baseline include foot sensation (touch) using cotton wool (abnormal if bilaterally impaired or absent), ankle reflexes (abnormal if bilaterally absent even on reinforcement) and vibration sensation measured using a 128 Hz tuning fork at the great toe (abnormal if bilaterally impaired or absent). We combined patients with an impaired or absent sensory response due to the smaller number of such patients when compared to those with a normal response. Patients with impaired or absent tuning fork sensation had similar VPTs (28.5 ± 12.7 V vs 27.2 ± 7.9 V, $p = 0.81$).

Type 1 diabetes mellitus was defined by our computer as age of onset of diabetes < 40 years. Insulin requirement within a year of diagnosis or ketosis at presentation were also required for the definition in the present study. Details of eye fundus examination (through dilated pupils where possible); HbA_1 (Corning method, 'non-diabetic' reference values 5.4 to 7.6 %, inter-assay coefficient of variation less than 5 %); dipstick urine test results (Albustix) and smoking and alcohol history were also entered into the database. Entry of height and weight were automatically transformed into a body mass index (BMI). Retinopathy was present if patients had one or more microaneurysms, exudates or preretinal haemorrhages (background) or had proliferative changes (proliferative). Smoking risk was assessed by comparing outcome in smokers and non-smokers at baseline, and by calculating the average lifetime smoking years in patients with and without morbidity events at review. Alcohol consumption in our clinic was categorized as nil, trivial (≤ 1 unit week^{-1}), moderate (≤ 6 units day^{-1}), heavy (> 6 units day^{-1}). For this study, patients were grouped as alcohol users (any degree) or non-users.

Clinical examination and data entry at baseline were performed by an endocrine consultant, senior registrar or research fellow in diabetes, using a computer terminal live during the consultation. Direct data entry, validated by the software, has ensured that since 1982 the quality of data entered is high (estimated error rate between 1 and 2 %). One formal audit on data quality revealed an error rate of < 2 %.

Table 1. Baseline characteristics of patients in cohort (1982–85)

Method of patient follow-up in 1995	Reviewed	Questionnaire	Lost to follow-up	Died
n	405	166	167	247
Mean years of age (range) (yr)	46.3 (14–77)	43 (6–75)	48.2 (9–87)	64.6 (23–85)[b]
Duration of diabetes (range) (yr)	4.7 (0–45)	4.4 (0–30)	6.3 (0–40)	5.2 (0–50)
Toe VPT (V)[a]	12.4 ± 5.7	12.4 ± 5.9	14.2 ± 7.4	20.7 ± 9.8[b]
Toe standard deviation score > 1.96 (%)	5.2	5.4	5.9	10.1[b]
HbA_1 (%)[a]	12.2 ± 2.7	11.5 ± 2.4	12.0 ± 2.6	12.4 ± 2.6

[a] Mean ± SD.
[b] Denotes significant difference at the $p < 0.05$ level (single factor ANOVA).

In 1995, 405 of the original cohort of patients (41.1 %) were successfully recruited and made a special visit to the hospital for re-examination. They were all seen by one observer (DVC). Toe VPTs (single site in patients with amputations) were repeated on all patients and the clinical portion of the Michigan Neuropathy Screening Instrument (MNSI) was used as an alternative validated measure of neuropathy. A MNSI score >2 identifies patients with diabetic neuropathy.[13] Ulcerations were defined as any full-thickness penetration of the dermis of the foot. Information on previous foot ulceration was obtained from self-reporting and from the computerized clinic records available since the baseline visit. Out of the 405 patients recruited for the study, 260 patients (64.2 %) had been last reviewed in clinic between January 1993 and December 1995. Patients are generally reviewed in our clinics on a 6-monthly basis and information on any abnormality in foot examination is recorded on the computer. The remaining 145 patients (35.8 %) had last attended the clinic prior to January 1993, mainly due to movement to a different locality, and out of these 60 % were last reviewed during or after 1990 and 40 % prior to 1990. Patients who had not recently attended were traced through the Family Health Services Authority (FHSA) and the National Health Service Central Register (NHSCR) held by the Office of the Population, Censuses and Surveys (OPCS). Both of these registers are now linked and computerized and provide a national network. The OPCS has a research unit that can provide (subject to ethical approval) information about vitality and locality for research purposes.

In 166 patients (16.8 %) who were unable to come to the hospital, information on foot ulcers and amputations was obtained by questionnaire sent to the patients via their General Practitioner. A further 247 patients (25.1 %) had died. Follow-up information was unavailable in 167 patients (17.0 %) either because patients were untraceable or they had left the country (Table 1). Only patients who were re-examined in the clinic were included in this analysis, due to the possible inaccuracies related to reporting on foot ulcers by patients answering a questionnaire. The baseline characteristics of the 405 patients reviewed in our study were compared to the rest of the patients in the cohort.

For a case–control study of risk factors for foot complications, 20 patients with either ulcers or amputations (cases) were individually matched in a 1:3 ratio, with 3 control diabetic subjects without foot complications for age, sex, and ethnic group. Five 'cases' could not be matched and were excluded. Although the overall number of subjects is relatively large, the number of cases observed is small. For this reason patients with ulcers and amputations were considered jointly.

The linkage of the Diabeta Register to the NHS Central Register and recruitment and follow-up examination of patients was approved by the St Thomas' Hospital and OPCS Ethics Committees.

Statistical Analysis

The summary statistic for each risk factor is the odds ratio (OR). The odds ratios are quoted with a univariate 95 % confidence interval and a *p*-value based on the full fitted model associated with an OR of 1. The interpretation of an odds ratio is straightforward for all discrete factors. For continuous factors the OR quoted is per one unit increase except for 'duration of diabetes' which is reported per 10 years of diabetes since diagnosis. We calculated univariate odds ratios, hence interaction between any factors was not considered, with the exception of the duration of diabetes, which was always included with each factor so as to adjust for its effect. The decision to use univariate odds ratios was deliberate, as with such a small number of cases the calculation of interactions was likely to be very inaccurate. All analyses were conducted with logistic regression, using the logistic procedure of the SAS system.[14] Sensitivity and specificity values were also obtained using the CTABLE option with prior probabilities set to the observed frequency of cases.

Single factor ANOVA was used to compare baseline characteristics of the 405 patients recruited for our study with those answering a questionnaire or lost to follow-up, and with patients who died.

Results

There was no significant difference in baseline VPT (and 'standard deviation score') or HbA_1 between patients reviewed for the study and those answering a questionnaire or those lost to follow-up; this rendered all the patients in the cohort who were still alive in a similar risk category. As expected, patients who subsequently died were significantly older than their counterparts but, of greater interest, they had a higher prevalence of an abnormal age-corrected VPT at baseline (Table 1).

Twenty-five (6.2 %) of the 405 patients reviewed in 1995 developed foot or toe ulcers ($n = 11$, 2.7 %) or underwent an amputation ($n = 14$, 3.5 %) between January 1982 and September 1995. None of these patients had had foot ulcers or amputations at or prior to the baseline visit.

All patients included in the case-control analysis had at least one clinically palpable pulse in each foot at the baseline visit. Their clinical characteristics at baseline are in Table 2. In the 14 patients who had lower limb surgery, 10 had toe or forefoot amputations and 4 had a below-knee amputation. In the ulcer-forming patients, all but 3 patients had plantar ulcers present at the review visit in 1995. The other 3 patients gave a history of previous ulcers in the weightbearing area of the feet and 2 had ankle Charcot deformities. Patients with lower extremity complications had marked neuropathy at review (Cases vs controls; VPT 44.5 ± 6.0 V vs 20.5 ± 9.2 V, $p < 0.0001$; MNSI 5.4 ± 1.0 vs 1.5 ± 1.1, $p < 0.0001$).

The OR for lower extremity complications developing up to 14 years after the baseline visit was 4.38 (CI 1.11–

Table 2. Baseline characteristics of patients entering study

	Ulcer/amputation patients	Controls	*p* value
n	20	60	
Diabetes duration (yr)[c]	9.7 (0–37)	4.1 (0–34)	0.02
Males	12 (60)	36 (60)	[a]
Age (yr)[c]	50.5 (28–61)	50.1 (16–72)	[a]
Type 1 DM	7 (35)	14 (23.3)	0.75
Caucasian	18 (90)	54 (90)	[a]
Asian	1 (5)	3 (5)	[a]
Afro-Caribbean	1 (5)	3 (5)	[a]
Abnormal clinical test	9 (45)	10 (16.6)	0.006
Toe VPT[b]	25.5 ± 10.1	12.5 ± 5.7	0.02
Toe 'standard deviation score' (SDS) > 1.96 SD	9 (45)	4 (6.7)	0.01
HbA_1 (%)[b]	12.5 ± 2.4	11.2 ± 2.7	0.016
Retinopathy (any)	8 (40)	9 (15)	0.20
Proteinuria (≥1+)	3 (15)	2 (3.3)	0.30
BMI (kgm^{-2})[b]	29.9 ± 3.7	28.0 ± 5.1	0.08
Height (cm)[b]	172.2 ± 10.9	167.8 ± 6.8	0.14
Smokers	7 (35)	12 (20)	0.34
Lifetime smoking years[c]	21.5 (0–57)	14.9 (0–57)	0.15
Alcohol use	12 (60)	42 (70)	0.70

Data are *n* (%) or otherwise specified. Paired statistical tests were performed using logistic regression.
[a] Patients were individually matched for these characteristics.
[b] Mean ± SD.
[c] Mean (range).

17.26, $p = 0.01$) for an abnormal age-adjusted toe VPT ('standard deviation score' > 1.96) and 2.3 (CI 1.00–5.20, $p < 0.01$) for one or more abnormalities in reflexes, touch, or tuning-fork vibration. Mean toe VPT at baseline in patients with subsequent morbidity events was higher than in controls (25.5 ± 10.1 V vs 12.5 ± 5.7 V, $p = 0.02$). The sensitivity and specificity in predicting outcome were 70 % and 72 %, respectively, for VPT and 55 % and 70 % for clinical testing. All 3 clinical tests showed the same sensitivity (55 %) and similar specificity (reflexes 70 %, touch 72 %, vibration 72 %). The OR for complications also doubles for every 10 years of diabetes ($p = 0.02$). Glycated haemoglobin at baseline was significantly higher in patients with subsequent foot complications (HbA_1 12.5 ± 2.4 % vs 11.2 ± 2.7 % in controls, $p < 0.02$) and was also a risk factor for such events (OR 1.30, CI 1.01~1.66; $p < 0.02$). HbA_1 at review had improved in both groups (9.1 ± 2.3 and 9.8 ± 2.0 %). These and other potential risk factors are highlighted in Table 3.

Smoking and alcohol consumption were not significantly correlated with the development of foot problems. Although high ORs were obtained for both retinopathy (background and proliferative) and overt proteinuria at baseline, these failed to reach statistical significance. Height and body mass index (BMI) were not associated with foot complications. There was no significant difference in drug or insulin treatment between the two groups. A history of hypertension obtained at review was not associated with morbidity events.

Discussion

Our study represents one of a few attempts to evaluate the risk for lower extremity ulceration or amputation. To our knowledge this study is unique in its representation of a large sample of 405 patients seen at a single hospital clinic, who were then reviewed 12 years later. Bias in patient recruitment was minimal, as shown by the common clinical characteristics shared by patients in our study and those in the cohort who were still alive but were not reviewed. Patients were also matched to minimize age-related and socio-cultural differences. In our case–control study, the potential controls covered a wider demographic base than the demographic base of the cases. Case–control matching reduced the confounding effect that such a different demographic make-up may have on the significance of the particular risk factors studied. No satisfactory matches could be found for 5 patients, and these were excluded to be sure that they were not cases because of unusual age, sex, and ethnic group.

In patients who were reviewed in 1995, not all had continued to attend our clinic after the baseline visit, some having moved out of the hospital catchment area. This highlights the problem in undertaking such long-term studies particularly in patients attending an inner city hospital. However, there was no significant difference in the total number of clinic attendances between the cohort of patients with morbidity and the control diabetic subjects. This is important as an indirect index of

Table 3. Risk factors for ulcers and amputations: logistic regression model

Predictor	OR	Lower	Upper	*p* value
Age (per year)	0.77	0.02	23.9	0.64
Duration (per 10 years)	2.10	1.11	4.30	0.02
Type of diabetes	0.70	0.10	3.82	0.75
Insulin treatment	3.47	0.76	15.7	0.07
Tablet treatment	3.56	0.07	191.8	0.24
HbA_1 (per % increase)	1.30	1.01	1.66	0.016
Height	1.05	0.97	1.14	0.14
BMI	1.08	0.95	1.23	0.08
Background retinopathy	2.23	0.53	9.42	0.21
Proliferative retinopathy	3.10	0.62	15.40	0.10
Proteinuria (≥1+)	2.01	1.01	5.24	0.27
Abnormal clinical test[a]	2.30	1.00	5.20	0.006
Abnormal VPT (SDS > 1.96)	4.38	1.11	17.26	0.01
VPT (per volt increase)	0.91	0.77	1.08	0.02
Hypertension	2.67	0.30	23.53	0.22
Smoking	1.79	0.52	6.10	0.34
Alcohol	0.89	0.51	1.57	0.70
Number of visits	0.96	0.90	1.03	0.18

[a] One or more abnormalities in reflexes, touch and vibration.

opportunity for access and of the quality of care which both groups of patients received over the 12-year period, reflecting one of the strongest features of the UK National Health Service (NHS).

Patients were initially examined by different observers at baseline under non-study circumstances and there were no written criteria on defining clinical observations or on measurement of VPT. All observers were however career diabetologists who worked together in the same diabetes clinic and had at least 3 years of postgraduate diabetes experience and training. Although there is an inevitable interobserver variability, VPT measurements appear very reproducible and relatively observer independent.[11,15]

VPT 'standard deviation scores' were clinically more useful and more predictive than raw VPT readings (V), as shown by the stronger correlation obtained for the former in the regression analysis (Table 3). To our knowledge, this study is the only one to provide data on the sensitivity or specificity of these tests. Their rather low sensitivity and specificity may be related to various factors in the study. Repeated testing (e.g. annually) after the baseline visit may have detected VPT abnormalities in patients who had normal measurements at baseline but subsequently developed complications. Similarly, control patients who tested positive at baseline (6.7 %) may have run into problems after the study was completed.

Age-adjusted VPT measurements are quick and easy to do and can help identify patients at risk of future morbidity events. The known relationship of VPT to age can be explained by age-related regressive changes of nerve structures.[16] In a 4-year prospective study, a cut-off toe VPT > 25 V was strongly associated with the risk of foot ulceration.[17] This study was however performed in patients attending a diabetes foot clinic, in patients likely to be at particularly high risk for foot ulceration. In contrast, we have evaluated the role of such tests in patients attending a routine diabetes clinic.

None of the patients in our study had evidence of foot ulceration at baseline. Collection of information on prior foot ulceration at baseline visit may not be entirely reliable. Similarly, patients, especially those in whom follow-up visits after baseline were sparse, may have forgotten about a minor foot ulcer that had healed during the course of the study. Overall, however, patients interviewed were generally able to recall the occurrence of previous foot problems with reasonable confidence.

In a 32-month prospective study, Rith-Najarian *et al*. showed that ulceration and amputation rates correlated strongly with a simple scoring method based on clinical examination.[18] Vibration perception using a 128 Hz tuning fork and ankle reflexes both have a high degree of reproducibility and sensitivity in the diagnosis of diabetic neuropathy.[19,20] Although we have shown that at least one of these clinical abnormalities carries a 2-fold risk of ulceration or amputation over a 12-year period, the sensitivity of any of these tests in predicting outcome was poorer than for VPT.

Although all patients with subsequent complications had marked neuropathy at review, some patients would have also developed significant lower limb ischaemia during the study. All patients with complications and controls had at least one clinically palpable pulse in each foot at the baseline visit. Palpation of foot pulses is a useful screening test, but by itself is a poor quantitative measure of the peripheral vascular supply. Besides, neuropathy is probably an earlier clinical manifestation in patients with subsequent neuro-ischaemic complications, and its detection by the methods outlined helps to identify such high risk patients.

Glycaemic control at baseline was worse in patients

subsequently developing ulcers than in control subjects who did not get problems. At review, glycaemic control in patients with morbidity events had improved in both groups of patients so it was poor glycaemic control at baseline that was associated with a worse outcome. In another study, mean blood glucose levels at baseline were also associated with an increased amputation risk in Pima Indians.[21]

Although retinopathy and proteinuria at baseline were associated with high ORs for lower extremity complications, significance at the 5 % level was not achieved. This may be related to the relatively short duration of diabetes (mean 4.7 years) at baseline for these complications to reach prognostic significance. Both retinopathy and kidney disease have been related to increased amputation in other studies.[21,22]

Our study failed to show any association between foot complications and smoking or alcohol consumption. Although smoking has been considered a strong risk factor for peripheral vascular disease,[23–25] it does not appear to contribute substantially to the excess risk of amputation in diabetes. In our study patients were grouped as smokers and non-smokers at baseline, so that the effect of the duration and degree of smoking on outcome may have been overlooked although in separate analyses of the entire Diabeta database there is little if any evidence of an adverse effect of smoking on vascular disease (Sönksen, unpublished observations). In the Wisconsin study, smoking was predictive of foot ulceration and amputation in patients diagnosed $<$ age 30 years but not among older-onset diabetic patients.[26] Other studies have failed to show an association between smoking and amputations.[22,27]

There was no relationship between admitted alcohol consumption and risk of foot complications. Other studies have not shown an association between alcohol consumption and amputation.[27,28]

Age-adjusted VPT measurements show overall better sensitivity than clinical tests and although repeat testing (e.g. annually) is likely to improve their predictive power, further studies are needed. To our knowledge no similar comparative predictive data are currently available in the literature and we recommend that VPT standard deviation scores should be an integral part of the annual review visit. Patients screening positive should be regarded as 'at risk' and should be entered into a structured foot care programme.

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Coppini DV, Young PJ, Weng C, Sönksen PH. Risk factors associated with the development of end stage peripheral neuropathy: a 10–13 year follow-up study (Abstract). *Diabetic Med* 1996; **13** (suppl 3) P85.

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